Using cannabinoids to explore the Cognitive Processes involved In the development of Psychosis

Study acronym: CPIP

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Protocol Synopsis

Study title	Using cannabinoids to explore the Cognitive Processes involved In the development of Psychosis
Study acronym	CPIP
Study type	Non-CTIMP Experimental Study
Sponsor	King's College London
Chief Investigator	Prof Philip McGuire
REC number	Health & Social Care Research Ethics Committee A (HSC REC A) Reference Number: 20/NI/0074
Study design	A randomised, double-blind, placebo-controlled, 3-arm cross-over experimental study
Primary Objective	To explore the cognitive processes involved in the development of four key psychotic symptoms (delusions, auditory hallucinations, persecutory beliefs and reduced motivation) by comparing the effects of Δ9-

	tetrahydrocannabinol (THC) alone, THC & cannabidiol (CBD) and placebo in an enriched sample of cannabis smokers with established psychotic symptoms.
Secondary Objectives	The secondary aims are to compare the effects of THC and THC/CBD with placebo for the following outcomes: 1. Cognition (including verbal learning, delayed recall, working memory) 2. Intermediate cognitive-psychotic processes involved in the development of specific psychotic phenomena: a. Auditory hallucinations b. Delusions c. Persecutory beliefs d. Reduced motivation 3. Subjective and objective psychotic experiences 4. Other subjective experiences 5. THC, CBD and metabolite plasma levels 6. Plasma endocannabinoid levels and potential biomarkers and inflammatory markers
Primary Endpoint	Difference in delayed verbal recall, as measured by the Hopkins Verbal Learning Test, between placebo/placebo and placebo/THC; and between placebo/THC and CBD/THC).
Secondary Endpoints	All measures will be collected at baseline (practice session) and then during each of three test conditions. Endpoints will be the difference between the three drug test conditions (placebo/placebo; placebo/THC; CBD/THC). 1. Cognition ○ HVLT-R Immediate verbal recall ○ Forward and reverse digit span 2. Intermediate Processes ○ White Noise Task ○ Jumping to Conclusions Task ○ Advice Taking Task ○ Effort Expenditure for Rewards Task 3. Psychotic experiences ○ Positive and Negative Syndrome Scale (PANSS) ▪ Positive subscale ▪ Negative subscale ○ State Social Paranoia Scale (SPSS) 4. Other outcome measures ○ State-Trait Anxiety Inventory (STAI-S) ○ Drug experience preference

	○ Visual analogue scales: • Feel drug effect • Like drug effect • Want more drug • Thinking clearly • Tired • Excited • Want to talk • Anxious • Relaxed • Happy • Irritable • Suspicious • Hearing voices • Dry mouth • Hungry 5. The difference in plasma levels of THC, CBD, and their metabolites 6. The difference in plasma endocannabinoid levels and potential biomarkers and inflammatory markers
Sample size	The study aims to achieve 30 complete datasets. Accounting for an estimated 25% drop-out rate it is expected to recruit 40 participants.
Summary of eligibility criteria	Inclusion: i. Age 18-65 years. ii. Clinical diagnosis of schizophrenia (i.e. documented as such in the patient's clinical records and satisfying ICD-10 criteria for F20) iii. Clinically stable for at least three months (since discharge from hospital, home treatment team, or prior clinical deterioration, and with agreement from the patient's responsible clinician) iv. Regular (at least weekly) cannabis use for the past 3 months or more v. Evidence from either clinicians or from the patient that cannabis use exacerbates their symptoms or increases their risk of relapse vi. Treatment with regular doses of antipsychotic medication for at least 1 month, confirmed by a blood test at the baseline visit, and with the participant agreeing to be maintained at a stable dose over the course of the experiment vii. The participant agrees to abstain from cannabis use for at least 24hours prior to study visits viii. The participant is willing to have an intravenous cannula inserted to collect blood samples on experimental visits ix. Sufficiently fluent English x. Providing written informed consent

	Exclusion: xi. Extremely frequent cannabis use/high daily use as judged by the study psychiatrist xii. Dependence on alcohol or illicit substances other than cannabis as defined by ICD-10 xiii. Pregnancy (current or planned) or breastfeeding xiv. Physical health disorder or another mental health disorder that the study psychiatrist judges may influence the patient's ability to tolerate the procedure, or that may alter the results of the study. xv. Taken part in any drug study within the last 3 months or taking part in another study over the course of the trial xvi. Drug sensitivity/allergy to cannabis or Lorazepam xvii. Unlikely to be able to complete the study sessions for any reason, as judged by the study psychiatrist Additional criteria which must be met on experimental visits xviii. Negative alcohol breath test xix. Negative urine drug screen (apart from cannabis and prescribed medication) xx. Negative urine pregnancy test xxi. Stable mental state as judged by the study psychiatrist
Study drug, dosage and administration	Participants will be administered 1000mg CBD orally or a matching placebo. 3 hours later they will inhale a dose of THC (initially set at 10mg, though with option to adjust this dose as the trial progresses). GMP approved cannabis plant material (typical batch release specification 22% THC) provided by Bedrocan BV, Netherlands; will be administered using a Volcano Medic Vaporizer (Storz & Bickel), Germany.
Version and date of final protocol	Version 1.0 [10/02/2020] Version 1.1 [03/03/2020] Version 1.2 [21/05/2020] Version 1.3 [15/06/2020]
Version and date of Protocol Amendments	Version 2.0 [26/06/2020]

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1. Summary

Psychotic disorders cause distressing symptoms and severely impact quality of life (Packer et al., 1997). The development of new treatments for these disorders has been limited by our incomplete understanding of the cognitive processes which underlie psychotic symptoms (Adams et al., 2013). Studies in healthy controls have shown that pre-treatment with cannabidiol (CBD) can counteract Δ9-tetrahydrocannabinol (THC) induced psychotic symptoms without significantly modifying other subjective effects (Englund et al., 2013) (Haney et al., 2016). THC and CBD are therefore ideal pharmacological probes to explore the cognitive processes underlying specific psychotic experiences (Paparelli et al., 2011). Comparing the effects of THC with THC/CBD will allow us to start to disentangle the processes behind the development of specific psychotic symptoms such as auditory-verbal hallucinations, delusional beliefs, persecution and amotivation (Volkow et al., 2016).

This study will recruit a carefully selected population of schizophrenia patients known to experience non-affective psychotic phenomena when self-administering cannabinoids recreationally. Recruiting this population will help minimise affective and pseudo-psychotic phenomena which are common in healthy controls and other patient populations and therefore produce misleading results (McCarthy-Jones et al., 2014)(Waters and Fernyhough, 2017). Each participant will attend the laboratory on three occasions: an initial visit to check that they are safe to join the study, and three days of testing. Across the three testing days participants will, in a randomized order, be administered 1000mg CBD orally and then inhale cannabis containing 10mg THC, a oral placebo and then inhale cannabis containing 10mg THC, and an oral placebo and inhale placebo cannabis. The THC administration will follow a standardised inhalation procedure using a medical-grade vaporizer device. Participants will then complete a series of standard cognitive tasks as well as tasks which explore four key psychotic phenomena: the White Noise Task (Galdos et al., 2010), the 'Jumping to Conclusions' Beads Task (Moritz and Woodward, 2005), Advice Taking Task (Diaconescu et al., 2019) and Effort Expenditure for Rewards Task (Treadway et al., 2009).Finally, measures of subjective and objective psychotic phenomena as well as measures of other relevant subjective states (i.e. mood, anxiety, pleasure, hunger) will be collected.

The study will be carried out at the NIHR-Wellcome Trust Clinical Research Facility at King's College Hospital by researchers who have experience of testing cannabinoid compounds in the acute setting and working with people with psychotic disorders. All participants will be individuals who already smoke cannabis regularly so that they are not exposed to any additional harm. The researchers will closely monitor those taking part to make sure that they are well, both during the visits and for several weeks afterwards. The study will comply with the Declaration of Helsinki and will be conducted in the principles of Good Clinical Practice (GCP). It will be reviewed and approved by a relevant Research Ethics Committee (REC).

2 Objectives

2.1. Primary objective

To explore the cognitive processes involved in the development of four key psychotic symptoms (delusions, auditory hallucinations, persecutory beliefs and reduced motivation) by comparing the effects of Δ9-tetrahydrocannabinol (THC) alone, THC & cannabidiol (CBD) and placebo in an enriched sample of cannabis smokers with established psychotic symptoms

2.2. Secondary objectives

The secondary aims are to compare the effects of placebo/THC and THC/CBD with placebo/placebo for the following outcomes:

1. Cognition (including verbal learning, delayed recall, working memory)
2. Intermediate cognitive-psychotic processes involved in the development of specific psychotic phenomena:
    a. Auditory hallucinations
    b. Delusions
    c. Persecutory beliefs
    d. Reduced motivation
3. Subjective and objective psychotic experiences
4. Other subjective experiences
5. THC, CBD and metabolite plasma levels
6. Plasma endocannabinoid levels and potential biomarkers and inflammatory markers

3 Trial Design

3.1 Trial Design

Randomised, double-blind, placebo-controlled, 3-arm, cross-over, within-subjects study.

The study includes one baseline visit followed by three experimental visits, separated by at least one week.

3.2 Study Flowchart

	Initial Brief Screening	Baseline Visit	Experimental Visits 1-3
Participant information and		X	
Informed consent		x	
Physical examination		X	
Demographic and clinical information	X	X	
Physical Observations		X	X
Alcohol, Drug and Pregnancy Tests		X	X
Blood sampling		X (antipsychotic level only)	X
Cannula			X
CBD/placebo administration			X
THC administration			X
Cognitive and psychopathological testing		X	X
Sobriety test		X	X
Follow-up call (+ 1 day)			X
Follow-up call (+7-10 days)			X

3.3 Recruitment

The research team will contact local clinical services (ie. inpatient wards and community mental health teams (CMHTs)) and ask them to identify patients who are likely to meet the study's inclusion criteria. Clinicians will then ask potential participants if they agree to be contacted by the study team. The researchers will also utilise the South London and Maudsley NHS Foundation Trust (SLaM) Consent for Contact initiative in order to recruit Trust patients and will follow the related Trust policy. The researchers will then contact potential participants by telephone or in person to explore their eligibility for the study and answering any questions they have about what participation in the study entails. The researchers will also obtain consent from the participant for the research team to review their clinical notes and discuss their history with their clinical team. If

the participants' responses to the initial questions are satisfactory, and there are no issues identified from the review of their clinical notes or discussion with the clinical team, the participant will be invited for a Baseline visit and be provided with a Participant Information Sheet (PIS).

3.3.1 Inclusion Criteria

Each participant must meet **ALL** of the following criteria:

i. Age 18-65 years
ii. Clinical diagnosis of schizophrenia (i.e. documented as such in the patient's clinical records and satisfying ICD-10 criteria for F20)
iii. Clinically stable for at least three months (since discharge from hospital, home treatment team, or prior clinical deterioration, and with agreement from the patient's responsible clinician)
iv. Regular (at least weekly) cannabis use for the past 3 months or more
v. Evidence from either clinicians or from the patient that cannabis use exacerbates their symptoms or increases their risk of relapse
vi. Treatment with regular doses of antipsychotic medication for at least 1 month, confirmed by a blood test at the baseline visit, and with the participant agreeing to be maintained at a stable dose over the course of the experiment
vii. The participant agrees to abstain from cannabis use for at least 24hours prior to study visits
viii. The participant is willing to have an intravenous cannula inserted to collect blood samples on experimental visits
ix. Sufficiently fluent English
x. Providing written informed consent

3.3.2 Exclusion Criteria

If the participants **ONE OR MORE** of the following criteria they will be excluded from the study:

i. Extremely frequent cannabis use/high daily use as judged by the study psychiatrist
ii. Dependence on alcohol or illicit substances (other than cannabis) as defined by ICD-10
iii. Pregnancy (current or planned) or breastfeeding
iv. Physical health disorder or another mental health disorder that the study psychiatrist judges may influence the patient's ability to tolerate the procedure, or that may alter the results of the study.
v. The participant has taken part in any drug study within the last 3 months or taking part in another study over the course of the trial
vi. Drug sensitivity/allergy to cannabis or Lorazepam
vii. Unlikely to be able to complete the series of procedures and study sessions for any reason, as judged by the study psychiatrist

3.3.3 Withdrawal of Subjects

Participants are free to withdraw from the study at any stage for any reason. The researchers may withdraw the participant from the study up until they complete their final experimental visit if it becomes apparent that they do not meet all inclusion and exclusion criteria. The researchers may

also withdraw the participant due to adverse or serious adverse effects, protocol violations, administrative or other reasons.

The researchers will ask the participant why they have decided to withdraw and will explain that this data will be recorded anonymously. The participant will not be obliged to disclose their reasons for withdrawal. The participant will be able to withdraw their data until two weeks after the final study visit but will not be able to withdraw their data after this point.

3.4 Baseline visit

3.4.1 Consent

The baseline visit will be held at either the participant's CMHT or at the King's Clinical Research Facility (CRF). At the start of the visit the researchers will explain to the participant the aims and procedures of the study once more. The participant will be given time to re-read the PIS and to ask questions about the study. The participant will be informed about what will happen during the rest of baseline visit and experimental sessions including requirements regarding alcohol and other drug use during and between study visits as well as data protection and confidentiality issues. If consenting, the participant and researcher will then read and sign the consent form.

3.4.2 Assessment for Study Eligibility

To assess for eligibility the following assessments will be completed by the study psychiatrist:

i. Mini-International Neuropsychiatric Interview to screen for co-morbid (non-schizophrenia) mental illness
ii. Clinical interview covering medical, psychiatric and substance use histories
iii. Review of electronic health records (electronic Patient Journey System)
iv. Discussion with the participant's Responsible Clinician
v. Mental state examination
vi. A targeted physical examination depending on physical co-morbidities identified during the assessment

3.4.3 Collection of additional demographic and clinical information

The following information will also be collected through interview of the participant and assessment of their electronic health records:

i. Demographics: age, gender, ethnicity, education level, employment, marital status

ii. Clinical information
    a. Current and past diagnosed psychiatric and medical illnesses
    b. Current and past substance use
    c. Current and past prescribed medications including long-acting injectable formulations and clozapine
    d. Admissions to psychiatric hospital, their legal status under the Mental Health Act, their duration, and admission to psychiatric intensive care wards

e. History of being subject to a Community Treatment Order
f. Management by forensic mental health services
g. Custodial/prison sentences
h. Health of the Nation Outcomes Scale score (most recent)

iii. Cannabis-Experiences Questionnaire (CEQ). A questionnaire concerned with subjective experiences of cannabis (Barkus et al., 2006). It has 13 questions divided into three subscales: Pleasurable Experiences, Psychosis-Like Experiences and After-Effects.

iv. Drug Use Questionnaire (DAST-20). A simple, 20-question self-scoring test about illicit drug consumption.

v. Michigan Alcohol Screening Test (MAST). A simple, 22-question self-scoring test about alcohol consumption (Selzer et al., 1975).

vi. Fagerstrom Test for Nicotine Dependence (FTND). A simple, 6-question test of cigarette consumption (Heatherton et al., 1991).

vii. Wechsler Test of Adult Reading (WTAR). This tool is used to provide a measure of premorbid intelligence (Wechsler, 2001).

viii. Revised-Green Paranoia Thoughts Scale. A scale which comprises an eight-item ideas of reference and 10-item ideas of persecution subscale (Freeman et al., 2019).

ix. State Trait Anxiety Scale. This scale differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety." The trait scale will also be used as an outcome measure (Spielberger 1983).

i. Carbon monoxide breath test. This test uses a simple handheld device. Carbon monoxide levels can be used as a measure of nicotine dependence.

ii. Height, weight, body mass index, body fat content (%).

3.4.4 Assessment for eligibility to continue with baseline and experimental visits

As well as meeting the study's inclusion and exclusion criteria, participants must fulfil a number of additional criteria at the baseline and experimental visits before completing any outcome measures. If a participant does not meet these criteria the visit will be postponed. Depending on the individual circumstances, the investigators will consider whether failing these criteria will mean that a participant has to be withdrawn from the study.

i. Negative alcohol breath test
ii. Negative urine drug screen (apart from cannabis and prescribed medication)
iii. Negative urine pregnancy test
iv. Stable mental state, as judged by the investigator and in light of the participant's normal baseline symptomatology

3.4.5 Baseline Antipsychotic Level

During the baseline visit, a single blood sample will be collected to measure plasma levels of prescribed antipsychotic medication. The sample will be collected by the study doctor or CRF nurses in a 5ml EDTA vacutainer. Staff will aim to take a trough sample (i.e. at least 6 hours post dose). The samples will be processed locally at the King's College Hospital/ViaPath Toxicology Unit. If the result of the test implies poor or non-compliance with prescribed antipsychotic medication, the participant will be withdrawn from the study.

3.4.6 Practice of Experimental Procedures and Collection of Baseline Outcome Data

At the baseline visit, if no reasons for exclusion are identified, the participant will then practice the inhalation procedure (with air only) and complete the cognitive and psychological test batteries. The cognitive and psychological test batteries are completed at baseline to familiarise the participant with the outcome measures.

3.5 Randomisation & Blinding

On each experimental visit the participant will receive one of the three drug conditions (placebo/THC; CBD/THC; placebo/placebo). The order in which they are given the two active study conditions and placebo condition will be randomised across experimental visits. The randomisation will be double blinded to both researchers and participants. The Maudsley Pharmacy will prepare study drug and dispense it to a blinded researcher. A statistician at King's College London who is not otherwise connected to the study in any other way will produce a randomisation list which will be held at the Maudsley Pharmacy. Information on the allocation of participants to experimental arms will concealed from the study team until the study is completed.

3.5 Experimental visits

After successfully completing the baseline visit, the participant will be asked to attend experimental visits. To complete the study, a participant must attend three experimental visits (placebo/placebo; placebo/THC; CBD/THC). To allow for washout of the study drug, there is a minimum of one week between experimental visits.

3.5.1 Timetable

Experimental Visit Timetable	Event	Time post-completion of THC administration	Expected Time
Preparation & Baseline Psychopathological Testing	Pregnancy, Alcohol & Drug Testing Mental state review Cannula Insertion Blood sampling I Visual Analogue Scales I STAI-S I SSPS I PANSS I	-3.5hrs	10am-10.30am
CBD/Placebo	Oral CBD/Placebo Administration	-3hrs	10.30am
	Visual Analogue Scales II	- 2hours	11.30am
Light lunch	Light lunch Blood sampling II	-90min	12pm-12.30pm
THC Administration	Visual Analogue Scales III (pre-dosing) STAI-S II (pre-dosing) Inhalation Procedure	-30mins	1pm-1.30pm
Initial Assessments	Blood sampling III Blood sampling IV Visual Analogue Scales IV Blood sampling V	0min +5min +10min +15min	
Cognitive and Psychopathological Testing	Hopkins Verbal Learning Test (5min) Digit Span (5min) White Noise Task (7min) Beads Task (3min) Advice Taking Task (8 min) Hopkins VLT - delayed recall (2min) Visual Analogue Scales V (2min) Effort Expenditure for Rewards Task (10min) Blood sampling VI Visual Analogue Scales VI STAI-S III	+20min +45min +90min	1.50pm 2.15pm 3pm
End of day review and final outcome measures	Visual Analogue Scales VII SSPS II PANSS Interview II	+3.5hrs	5pm
Sobriety Assessment	Sobriety Assessment		

Discharge	Discharge	4hrs	5.30pm
			STAI-S: State-Trait Anxiety Inventory-State Scale SSPS: State Social Paranoia scale PANSS: Positive and Negative Syndrome Scale

3.5.2 Preparation

Before experimental visits the participant will be asked to:

- abstain from alcohol and cannabis for at least 24 hours before experimental visits
- abstain from other illicit drugs for at least 7 days before experimental visits
- eat their normal breakfast
- have their normal morning caffeine and nicotine
- take their normally prescribed medications

Upon arrival the participant will complete the eligibility tests described in section 3.3.4. If there is no reason to postpone the experimental visit the participant will have an intravenous cannula inserted for blood sampling and a baseline blood sample will be collected. Baseline vital signs (heart rate, blood pressure and, temperature) will also be recorded.

3.5.3 Administration of oral CBD/Placebo

The participant will then be administered oral CBD or a matching placebo. Previous studies have shown that oral CBD reaches peak plasma concentrations within 3 hours. Administration of vaporized THC will therefore be timed to occur 3 hours after administration of the CBD/placebo.

3.5.4 Inhalation Procedure

The cannabis containing THC and the placebo cannabis will be provided by Bedrocan BV, Holland. Bedrocan produce standardised cannabis plant material according to Good Manufacturing Practice and meet the European Medicines Agency's contaminant levels for products used in the respiratory tract. The products are regulated by the Dutch government's Office of Medicinal Cannabis at the Dutch Ministry of Health, Welfare and Sport. The specific product used in this study is called Bedrocan (typical batch release specification 22% THC, <1% CBD). The placebo contains the precise terpene profile of the original strain, with all cannabinoids removed to <0.2% of dry weight.

Initially, 10mg THC (or matching placebo) will be administered to each participant on every experimental visit. As the study progresses, it may become apparent that 10mg is not the ideal dose and that it should therefore be adjusted. It will be reduced if too many participants experience over-intoxication or adverse effects. It will be increased if the majority of participants are able to tolerate the drug but the effect of the drug on outcome measures appears to be limited. The range of doses will be between 5mg and 25mg (a justification for this range has been added to the addendum on study drug dosing [section 12]). The principal investigator must approve any change in dose. The maximum increase in dose at any one time is 5mg. Investigators will not be able tailor the dose on participant-by-participant basis. If the dose has been changed, already completed experiments will not count towards the total sample size (target: n=30).

The cannabis will be administered via the intra-pulmonary route using a standardised inhalation protocol which has been used in previous comparable studies. The cannabis is prepared and vaporized by nursing staff separate from the study team to maintain blinding to the type of cannabis being administered. The cannabis preparations will be vaporized at 210°C using the Storz-Bickel Volcano® Medic Vaporizer. This will vaporize the cannabis into a transparent polythene bag with a valve mouthpiece which prevents loss of drug between inhalations. This bag is then covered by a second non-transparent bag so that the cannabis vapor, the density of which may vary according to cannabis type, is not visible to the participants or researchers.

The inhalation procedure will start when the participant is standing. Participants will be instructed to inhale a medium size breath from the bag, hold their breath for 8 seconds, and then exhale. They will then wait another 8 seconds before taking another breath. They will repeat this process until the balloon has been emptied.

To ensure that the study drug is delivered to the participant this process will be repeated for a second time. The same cannabis plant material will be heated and vaporized for a second time and a second balloon with be filled with the remnants of the study drug. There will be a 1-2minute break between balloons. Once both balloons have been inhaled the participant will be seated or lying down in a bed.

Throughout the inhalation procedure the investigator will monitor the participant for adverse effects or over-intoxication. The details of the safety protocols and procedures are described below (section 3.7).

3.6 Outcome measures

3.6.1 Burden to participants

We have deliberately selected the fewest outcome measures required to adequately explore the cognitive and psychological aspects of four key psychotic symptoms (delusions, hallucinations, persecution, loss of motivation). Together, the cognitive and psychological outcome measures are expected take around 40minutes. Inhalation of 10mg THC leads to a reasonable or high level of intoxication for at least 90minutes. There is therefore no pressure to complete the tasks in rapid succession and participants will be able to take short breaks between measures.

3.6.2 Blood and urine collection, handling and analysis

Urine will tested using a bedside drug screen and a bedside pregnancy test. It will be disposed of immediately after this.

At the baseline visit, a blood sample will be taken to test for prescribed antipsychotic levels. The test will be completed by ViaPath and be processed according to standard clinical procedures.

On experimental visits, participants will have a venous cannula inserted for collection of blood samples. Blood samples will be taken before administration of CBD/placebo, 2 hours post CBD administration (30mins pre-THC inhalation) and at 0, 5, 15 and 90minutes after the end of the

THC/placebo inhalation procedure. Each sample will be collected in a 5ml lithium-heparin tube (green). Within 10min of collection, the samples will be centrifuged (3000rpm for 10minutes). The plasma will be decanted from the lithium-heparin tube into two screw-cap collection tubes and immediately placed in a -20^{o}C freezer. The stored samples will be anonymised with participant ID, visit number and time point. Only the research team will be able to link ID number to participant details. Once the final sample has been collected, the samples will be moved to a -80^{o}C freezer for longer term storage. Only plasma will be stored so that analyses can be completed. No human tissue will be stored at the end of the research, all tissues will have been disposed of in accordance with the Human Tissue Authority's Code of Practice

Plasma samples will later be analysed for the levels of prescribed antipsychotic, Δ9-THC, 11-OH-Δ9-THC, 11-COOH-Δ9-THC, CBD, 6-OH-CBD and 7-OH-CBD, potential biomarkers and inflammatory markers using high performance liquid chromatography–mass spectrometry at the King's College London Mass Spectrometry Facility according to their local procedures.

3.6.3 Cognitive measures

Hopkins verbal learning task – Revised

The investigator reads a list of 12 words to the participant. The participant is then asked to recall as many of the words from the list as they can remember. They repeat this process three times. 20-25 minutes later the participant is asked to recall as many of the words from the list as they can remember. Repetitions and intrusions (words recalled not part of the original list) are recorded for each trial. A different version of the task (i.e. a different list of nouns) will be used on each occasion. (Brandt 1991).

Forward and reverse digit span

In the forward digit span the investigator reads a string of numbers to the participant which the participant repeats back in the same order. If the participant is correct the length of the string of numbers increases by one. The task is ended when the participant fails to give the answer on two consecutive attempts. For the reverse task the participant must recall the list of numbers in reverse order.

3.6.4 Intermediate measures

White Noise Task

This task is designed to provoke illusions of speech in white noise (Galdos et al., 2010). Participants listen to 75 consecutive 1-second audio clips of three different types: white noise only, white noise + barely audible speech, white noise + clearly audible speech. Following each 1-second stimuli, participants indicate whether they heard something, nothing or if they are not sure.

Jumping to Conclusions (JTC) - Beads task

The JTC Beads Task examines the relationship between evidence gathering and delusion formation (Moritz and Woodward, 2005). Participants complete the task on a laptop. They are first shown two jars of beads: one mostly red jar (60 red beads & 40 blue beads) and one mostly blue jar (40 red beads &60 blue beads). The jars are then hidden and participants are shown a (pre-determined,

quasi random) sequence of beads apparently being drawn from either one of the two jars. After each draw, participants can either decide to make a decision about which jar they believe the beads are being drawn from or see another bead. Compared to healthy controls individuals with established delusional beliefs are known to make a decision significantly fewer beads have been drawn, a 'jumping to conclusions' bias.

Modified Advice Taking Task
This laptop task is a modified version of the advice-taking task used by Behrens and colleagues (Behrens et al., 2008) (Diaconescu et al., 2019). It provides a measure of social inference which is believed to play a key role in the development of persecutory delusions. On each trial participants try to predict a binary outcome (blue vs. green). They are offered two sources of information with each trial: a social cue (human advisor) and a non-social cue (pie-chart). The pie-chart displays different green-blue ratios (50:50, 55:45, 60:40, and 75:25) thus varying its certainty. Participants are informed that the advisor will vary their intentions to either help or obstruct the participant. They will also be told that the adviser does not have full information and could therefore make unintentional mistakes. Players accrued points with every correct prediction and are provided a reward depending on their overall success.

Effort Expenditure for Rewards Task (EEfRT)
This laptop task measures effort-related decision-making (Treadway et al., 2009). Participants must decide between two different effort options: a low-effort choice, in which a small amount of money was available to be won (50p), and a high-effort choice, in which a larger amount of money is available to be won. The low-effort choice requires 30 spacebar presses with the little finger of the non-dominant hand in 7 seconds. The high-effort choice requires 100 spacebar presses with the little finger of the non-dominant hand in 21 seconds. The probability that the participant will win the money for the task if they complete it successfully is presented to the participant before they make their choice. Participants complete 21 trials in total, and the trial order is randomized.

3.6.5 Psychotic symptom measures

State social paranoia scale (SSPS)
This is a 10-item instrument which measures persecutory thoughts (Freeman et al., 2007). The persecutory items (e.g. 'someone had bad intentions towards me') are presented among 10 neutral items and scored on a 5-point scale (do not agree – totally agree).

Positive and negative syndrome scale (PANSS) – positive subscale and negative subscales
The PANSS is the most common scale to measure psychotic symptoms and commonly used in schizophrenia research (Kay et al., 1987). The positive subscale includes the following symptoms: delusions, conceptual disorganisation, hallucinations, hyperactivity, grandiosity, suspiciousness and hostility. The negative subscale contains these symptoms: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The symptoms are scored on a 7-point scale from absent-severe. The PANSS is an investigator rated scale and is scored following a semi-structured interview and through observation of the participant during the experimental visit.

3.6.5 Other outcome measures

State-Trait Anxiety Inventory-State (STAI-S)

This is a 20-item scale which measures current state of anxiety (Spielberger 1983). Each item is scored from 1 (not at all) to 4 (very much).

Visual analogue scales (VAS)

These will be used to measure contemporary subjective experiences. The scales ranges will range from 0 to 10. The following scales will be used:

- Feel drug effect
- Like drug effect
- Want more drug
- Thinking clearly
- Tired
- Excited
- Want to talk
- Anxious
- Relaxed
- Happy
- Irritable
- Suspicious
- Hearing voices
- Dry mouth
- Hungry
- Vulnerable
- Threatened

As the study progresses, additional visual analogue scales may be added if it becomes apparent that relevant symptoms are not accounted for.

3.6.6 Next day effects

The day after each experimental visit, participants will be contacted by an investigator as part of the safety and follow-up protocol. During the call they will ask questions related to subjective effects and adverse events following the study visit.

The will also complete the following scales to measure contemporary subjective experiences. The scales ranges will range from 0 to 10. The following scales will be used:

- Feel drug effect
- Like drug effect
- Want more drug
- Thinking clearly
- Tired
- Excited
- Want to talk

- Anxious
- Relaxed
- Happy
- Irritable
- Suspicious
- Hearing voices
- Dry mouth
- Hungry

3.7 Safety

The research group at KCL has extensive experience in the experimental administration of cannabinoids and well-established procedures to manage adverse effects. The study will at the CRF which is based within King's College Hospital, a large teaching hospital. It is a short walk away from A&E and has access to all on-call acute medical support.

3.7.1 Baseline safety measures

At the baseline assessment, the participant will be assessed by a psychiatrist who is experienced in working with patients with schizophrenia and with using cannabis preparations in an experimental setting. The psychiatrist will also review the participant's electronic clinical record and discuss the inclusion of the participant with their responsible clinician (ie. Community Mental Health Team Consultant) and their care-coordinator. The care-coordinator and responsible clinician will be provided with the study's PIS and be able to discuss the study with the study psychiatrist. They will also be made aware of the dates of the experimental visits which their patient will be attending the study on. If the participant provides consent, the study team will also inform relevant friends, family or carers of the dates of their experimental visits.

3.7.1 Pre-THC Inhalation

On arrival at the laboratory, participants will complete the assessments described in section 3.3.4. Before the inhalation procedure, the investigator will talk to the participant about what to expect over the rest of the experimental visit.

3.7.2 Post-THC Inhalation

During inhalation the participant will stand next to a chair or bed so that if they feel lightheaded they are able to sit or lie down easily. If this occurs, the inhalation procedure will be paused and the participant will have their physical observations checked.

Physical observations (HR, BP, Temp) will also be collected at baseline, at 0, 5, 15 and 90minutes post-inhalation, and before discharge. If physical observations are of clinical concern, a study doctor, who will be present throughout testing, will continue to monitor their physical observations and overall well-being closely and seek appropriate specialist advice as required

Throughout the inhalation, the investigator continuously monitors for physical and psychological effects of the drug. If the participant appears to be experiencing unpleasant side effects or is

unlikely to tolerate the full dose of the study drug, the administration can be paused or halted at any time.

In the unlikely event of distressing side effects (e.g. paranoia, anxiety), rescue medication (lorazepam) will be made available. If symptoms are severe, antipsychotic medication can also be used.

SLaM Pharmacy will serve as the emergency code breaker. In the extremely unlikely case that a clinician requires blinded information from a participants' experimental visit, they can contact SLaM Pharmacy switchboard where they can speak to the on-call pharmacist for code breaking information at all times including out-of-hours. Out of hours, there may be a delay of up to three hours before the pharmacist is able to obtain the relevant information. The contact details for the SLaM switchboard will also be made available to participants.

3.7.3 Sobriety testing

At the end of experimental visits, participants will complete a series of sobriety tests. These will include examination of mental state by a psychiatrist and completion of the Standardized Field Sobriety Test Battery (heel-toe walking and turn, horizontal nystagmus, one leg stand test). These tests will also be completed at baseline to assess participants ability to complete them when sober and make reasonable adjustments on experimental visits if required.

Participants who are not considered to have fully recovered will be permitted to stay in the facility for as long as necessary. In the unlikely event that a participant's symptoms do not resolve by the end of the study session Participants who are not considered to have fully recovered will be permitted to stay in the facility for as long as necessary. In the unlikely event that a participant's symptoms do not resolve by the end of the study session, the following protocol will be adhered to:

1. The participant fails the sobriety test.
2. The study team will explain to the participant that they have failed the test and that they will have to remain under observation until the study psychiatrist agrees that they are psychologically fit to return home.
3. The participant will be able to repeat the sobriety tests and assessment with the study psychiatrist at regular intervals.
4. If it is likely that the participant will need to remain under observation for a significant period of time, the study team will inform the nurse in charge of the CRF of this issue. They will discuss how long the CRF is likely to remain open for.
5. The study team will also offer to contact a family member, carer or friend so that they can be informed that the participant remains under observation in hospital. The study team may contact the family member, carer, or friend without the participant's consent, if the participant had previously provided consent for such contact, they currently lack the mental capacity to make this decision and such action would be in their best interests.
6. If the participant does not agree to remain under observation, the importance of safety and continued observation will be explained to them. If they disagree with

study psychiatrists assessment, and request discharge from the unit, the study psychiatrist will consider assessing the participant for section 5.2 of the Mental Health Act.

7. If the CRF closes, the study team will transfer the participant to the A&E department at King's College Hospital. They will inform the Psychiatric Liaison Nurses in A&E and the on-call psychiatry SpR and consultant
8. Once the participant has been transferred to A&E, responsibility for their care will be taken over by SLaM.
9. If the participant is transferred to A&E or another inpatient ward, or is detained under the Mental Health Act, the study's Chief Investigator will be informed at the earliest opportunity.

3.7.4 Follow-up

Participants will receive two follow-up phone calls from the study team on day 1 and between days 7-10 after each experimental visit. The participants will be asked questions relating to their general well-being, sleep, mood, anxiety, psychotic symptoms, and adverse events. Normal clinical care will continue during the course of participation. If a patient becomes unwell during the study or its follow-up period, the study team will inform the participant's community mental health team to request appropriate clinical follow-up.

If a participant doesn't respond to an initial phone call from the study team, the following escalation protocol will be adhered to:

1. Repeat phone calls x2
2. Text message asking the participant to call the study team
3. If the participant has provided consent, the team will contact a family member, carer or friend and ask them to check that the participant is well, and request that the participant contacts the study team
4. If there has been no contact with the participant to confirm that they are well, the study team will contact the participant's care-coordinator and responsible clinician on the morning of the next working day. The study team will ask the care-coordinator and responsible clinician to follow their usual clinical protocol in such circumstances. At this point, the follow-up will be handed over to the Community Mental Health Team.

3.7.5 Covid-19

Local guidance (SLaM and King's College Hospital) on the management of SARS-CoV-2 will be followed throughout the study.

4. Trial Statistics

4.1 Sample Size

The relative effects of THC, CBD/THC and placebo have never been compared in this population previously. We chose a sample size (n=30) which we believe has adequate power to detect meaningful effects. In a two-tailed paired sample t-test, a sample size of n=30 has 80% power, at alpha=0.05 to detect an effect size of 0.53.In a study comparing the effect of THC relative to CBD/THC on psychotic symptoms in healthy volunteers[27], the effect size for increase in State Social Paranoia Scale was d=0.64. If the alpha is reduced to 0.025 (to account for two main comparisons for the primary outcome measure) the corresponding detectable effect size is 0.58. Assuming a drop-out rate of 25% (as in previous studies using this methodology), we plan to initially enrol n=40 patients.

4.2 Analysis

Study data will be analysed following the completion of data collection and database lock. For the primary analysis linear mixed models will be used, with fixed effects of experimental condition and random intercept for repeated measures within participants. For the primary outcome there will be two linear contrasts of interest, placebo/placebo vs. placebo/THC and placebo/THC vs. CBD/THC. Differences in the frequency of categorical data will be analysed using Pearson's Chi-square test or multilevel logistic regression as appropriate. Relationships between cognitive, intermediate and psychosis data will be analysed using Pearson's or Spearman's rank correlation coefficient. If data do not fit a normal distribution they will be analysed after appropriate transformation. We will present both effect sizes and tests addressing study hypotheses with statistical significance set at $p < 0.05$ (or $p < 0.025$ for reporting of two related comparisons as for the primary outcome). All tests will be two-tailed.

5 Participant reimbursement

Participants will be reimbursed for their time at a rate equivalent to the London Living Wage (£10.55/hour). The baseline assessment is expected to take 4 hours and each experimental visit is expected to take up to 8 hours, a total of 28 hours. The total payment for completing the study will be £295. The participant will be paid £30 for the baseline, £70 for experimental visit 1, £90 for experimental visit 2 and £105 for the final experimental visit. Participants who do not complete all study visits will be reimbursed for the number of study visits they have attended. Participant will be paid either in cash or via bank transfer as per their preference. For bank transfers, bank details will be taken from the participant at the end of the study and payment will be processed 2-4 weeks after the final study visit.

6. Trial Steering Committee

The trial steering committee will supervise the trial on behalf of the sponsor, ensuring that the study is conducted under good clinical practice (GCP). In addition the trial steering committee will monitor progress of the trial, monitor adherence to the protocol and monitor participant safety.

The trial steering committee will include Professor Philip McGuire, Professor John Strang, Dr Amir Englund and Dr Edward Chesney.

7. Access to Source Data and Documents

The researchers will permit study-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents.

8. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice (GCP) and in accordance with all applicable regulatory requirements. The study protocol, informed consent form, and participant information sheet will be submitted to an appropriate Research Ethics Committee (REC) and R&D for approval.

Should the protocol require a major amendment, the amended protocol will be sent to the REC and R&D for approval before the changes in the protocol will be implemented. Minor amendments (administrative or logistic) may be implemented immediately, and the REC will be informed of this in writing.

Written informed consent will be obtained from each participant before the initiation of any data collection or study related activity. Consent will be obtained in accordance with REC guidance and GCP and be performed by Edward Chesney or another psychiatrist.

9. Data Handling

The study will adhere to KCL's policy on data management, security and sharing.

Participants will provide written informed consent for the study team to access their medical records. The study team will review their electronic health record (ePJS) for the South London and Maudsley Trust and will also review the Local Care Record which accesses their primary care notes and records across King's Health Partners (ie. Guys, St Thomas, King's Hospitals).

We will ask participants to provide mobile phone numbers and/or email addresses so that we can contact them during the study. We will not request personal address details unless we are booking a taxi for them. If a participant requests, they will be contacted with the study outcome.

The Chief Investigator will act as custodian for the study data and all participant data will be anonymised. Data will be collected using source data questionnaires (pen and paper) and laptop computers (cognitive tasks) on study visits. Each study participant will be given a study ID consisting of a 3 digit number preceded by the study acronym "CPiP" (e.g. CPiP002). Source documents and electronic data records (SPSS or Excel) will be named with this ID. The source documents will be kept in locked cabinets within access-card locked rooms; electronic data will be backed up onto encrypted external hard-drives.

Only the study research team will have access to participant's non-anonymised personal data during the study. Study data will be analysed at the IoPPN, King's College London, by the research team including study statistician. Data files which will be analysed will contain the participant ID number and contain no identifiable personal data. If participant's bank details are used to provide payment, the information will be not be stored for any longer than necessary and will be destroyed at the earliest opportunity according to standard departmental procedures.

Research data will be stored for a minimum of 10 years following the completion of the study. Case report forms will be scanned so that they can stored electronically along with other data from the study. We plan to store the data on King's Research Data Management system.

10. Publication

The trial protocol will be published in advance on Open Science Framework (www.osf.io/). Hypotheses for each outcome measure will also be pre-registered. It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. Where appropriate, the results will be disseminated to the general public by means of press releases, posts on social media and at public engagement event. As the results of the study may be valuable to public policy, the results may also be shared with governmental advisory groups such as the ACMD. Individual participants will not be identifiable in publications.

11. Finance

The trial is being funded by the National Institute of Health Research Award NIHR300273 (£412,000).

12. Addendum: Rationale for THC and CBD doses and routes of administration

Rationale for CBD dosing and administration route

Intravenous administration of CBD is not an established route. Inhalation of CBD is ineffective at higher doses due to coughing(Solowij et al. 2019). We therefore chose to administer CBD orally.

A recent systematic review of the pharmacokinetics of cannabidiol highlighted the paucity of data from human studies(Millar et al. 2018). The best data, is probably from submissions for EMA approval of epidiolex (cannabidiol oral solution) which says:

> 'Bioavailability of CBD was approximately 6.5 % following oral administration in fasting conditions. Due to significant food effect observed the bioavailability following administration with food can be expected around 14-25%.'
> (https://www.ema.europa.eu/en/documents/assessment-report/epidyolex-epar-public-assessment-report_en.pdf)

We are aware of the food effect of CBD and are requesting that our participants ensure that they eat their normal breakfast before experiments.

In a study of healthy volunteers, 600mg oral CBD led to a significant reduction in the proportion of subjects who developed psychotic symptoms (Englund et al. 2013). There have been two randomized controlled clinical trials of CBD as an add-on treatment for schizophrenia. In one 600mg daily was not effective at reducing psychotic symptoms(Boggs et al. 2018), in the other 1000mg was effective(McGuire et al. 2018). We therefore decided to administer 1000mg of CBD orally.

CBD reaches peak plasma concentration after around 3 hours after oral administration. We will therefore administer the CBD 2 ½ hours before the start of the inhalation procedure which takes up to 30 minutes.

Rationale for THC dosing and administration route

THC can be administered orally, inhaled or intravenously. During the preparation for this study, the study team interviewed patients who said that inhalation of vapor was the most acceptable route as it is the most similar to smoking, the standard route of administration for almost all users. Familiarity with smoking will mean that users are less likely to become over-intoxicated as they are able to titrate the study in their usual manner. There is also significantly less variability in absorption between individuals compared to oral administration. Vaporization is expected to deliver around 30-40% of the total THC dose to the participant (i.e. 3-4mg.)

In a recently completed study at King's College London (eCBD Study), a 10mg dose of THC was administered to healthy volunteers who were infrequent cannabis users (<1/weekly). The overall drop-out rate due to adverse events was 21% (12/58). Five of these were due to hypotension and one was due to vomiting (reactions more common in inexperienced users), while another participant dropped-out due to an anxiety disorder unrelated to the study. There were only three instances of over-intoxication and two negative emotional responses to the study drug, a total of 5/58 participants (9%).

An additional point is that we would expect regular users to have a much higher tolerance to THC. For example, in one study of frequent cannabis users (53% daily users, mean 21days/month), compared to placebo, a dose of 2.5mg THC IV caused a slight improvement delayed verbal recall, suggesting that these participants experienced withdrawal symptoms during the placebo arm(D'Souza et al. 2008).

The most useful information available comes from previous studies in patients with psychotic disorders. There are five relevant studies, three of which are discussed here (D'Souza et al. 2005)(Kuepper et al. 2013)(Henquet et al. 2006), while two neuroimaging studies unfortunately provide little information on either the psychological effects or safety of THC in this population (Whitfield-Gabrieli et al. 2018)(Vadhan et al. 2017).

D'Souza et al. used an IV preparation of THC in patients with schizophrenia who did not use cannabis regularly and were prescribed a regular antipsychotic (D'Souza et al. 2005). They compared two doses of THC: 2.5mg and 5mg, equivalent to around 7mg and 14mg of vaporized THC, with placebo. It is important to note that in this study, the IV THC was administered over only 2minutes. Unlike in the CPIP study, this would have prevented early termination of drug administration due to over-intoxication.

There study reported two adverse events related to the study drug:

> 'One subject who failed to disclose a remote history of untreated hypertension at screening experienced hypertension, anxiety, and paranoia after receiving 5 mg delta-9-THC'.
>
> 'One subject diagnosed with paranoid schizophrenia who did not like the effects of delta-9-THC withdrew consent after completing 2 test days and became paranoid about research staff and his clinicians.'

An increase in PANNS-positive score of 3 or more was considered significant. The 2.5mg dose triggered such a reaction in 80% percent of the patient participants (mean increase: 5, range: -2 – 11). The 5mg dose triggered a significant reaction in 75% of participants (mean increase: 5, range: 0 – 12)

Kuepper et al. administered 8mg THC via a vaporizer to 9 *medication-free* patients with a psychotic disorder(Kuepper et al. 2013). Six participants were daily cannabis users, one was a weekly user and two used it monthly or less. They reported no serious adverse events or drop-outs. There was little data on the psychological effects of the drug, but the study reported that THC induced significant increases in visual analogue scales, such as 'feeling high', and that there were no differences in these outcomes compared to two control groups (relatives of patients and healthy controls).

Henquet et al. administered THC to 30 patients with a psychotic disorder, 8 of whom were not prescribed an antipsychotic(Henquet et al. 2006). The dose used was 300ug THC/kg, equivalent to 21mg in a 70kg person. The THC was smoked in cigarettes containing tobacco. In another study comparing smoking of THC with vaporization, the subjective effects of 25mg smoked THC were similar to a 10mg vaporized dose (Spindle et al. 2018). Henquet et al. combined two other groups (relatives of patients and healthy controls) with the patients for all analyses preventing group specific inferences. The study did not report any adverse events.

Considering these studies together, we believe that 10mg THC inhaled via a vaporizer is a reasonable dose to use in patients with schizophrenia who are regular cannabis users and are prescribed antipsychotic medication. This dose is likely to trigger a short-lived, mild-moderate psychotic reaction in a reasonable proportion of participants. Since the THC can be administered over a period of 30 minutes, the likelihood of adverse events is reduced.

Rationale for the potential range of THC doses (5mg – 25mg)

Though we know that, compared with placebo, 10mg THC is likely to have a significant effect on outcome measures without compromising tolerability or safety, it is possible that an alternative dose is preferable. As the study progresses, the investigators may therefore adjust the dose of THC which subsequent participants receive. The range of 5mg to 25mg THC encompasses a range of doses used in previous studies. In studies of healthy controls who use cannabis infrequently doses as high as 21mg inhaled (Mason et al. 2019) and 25mg inhaled (Spindle et al. 2018) have been used with limited adverse effects and no serious adverse effects. Doses as high as 21mg smoked have been tested in patients with psychotic disorders (Henquet et al. 2006).The CPiP study includes participants who not only use cannabis regular but are also taking regular antipsychotic medication both of which reduce the effect of THC on cognitive and psychopathological outcomes. For example, in a study of regular cannabis users, 5mg THC IV (equivalent to 14mg inhaled) had a limited effect on cognition (D'Souza 2008).

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14. Signature

Chief Investigator *Print name*	Date